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Occupational contact dermatitis caused by *N*-butyl-1,2-benzisothiazolin-3-one in a cutting fluid

Jakob Dahlin and Marléne Isaksson

Department of Occupational and Environmental Dermatology, Skåne University Hospital, Lund University, S-205 02, Malmö, Sweden

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Isothiazolinone preservatives are used in several different water-based products, such as paints, metalworking fluids, and cosmetics. We present a case in which an isothiazolinone preservative, *N*-butyl-1,2-benzisothiazolin-3-one (BBIT; CAS no. 4299-07-4; Fig. 1), which has not previously been reported as a contact allergen, was found to cause hand eczema in a metalworker.

Case Report

A 35-year-old male CNC operator was referred to us in July 2014 because of hand eczema lasting for 5 months, and suspected to be work-related. At presentation, pulpitis was present on fingers 2 and 3 of both hands, especially on the left hand. The patient had worked in the present factory for 3 years, but had performed similar work previously. The patient claimed that his hand eczema always disappeared during time off work, such as vacations, and always recurred within a few days after he returned to work. He was patch tested with the Swedish baseline series (Chemotechnique Diagnostics, Vellinge, Sweden), the supplement to the baseline series used in Malmö, a metal series (Chemotechnique Diagnostics), an oil and cooling fluid series, and samples brought from the workplace by the patient, including a diluted and a concentrated metalworking fluid. Patch testing was performed with Finn Chambers® (diameter 8 mm) (SmartPractice, Phoenix, AZ, USA) covered with Scanpor® tape (Norgesplaster A/S, Vennesla, Norway). Readings were performed on day (D) 3 and D7, according to ICDRG criteria. The patient reacted only to the diluted metalworking fluid (Table 1). A workplace visit was performed to further scrutinize exposure to potential irritants and allergens, and new samples were taken for further patch testing, including circulated metalworking fluid at the use concentration of 13% from the patient's machine, unused metalworking fluid diluted to 6%, and grease. The concentrations of the metalworking fluids collected at the workplace visit were measured with a refractometer. The concentration of the metalworking fluid used at the workshop could vary between 5% and 15%, depending on the material to be tooled. New patch testing again showed positive reactions to the metalworking fluid (Table 1).

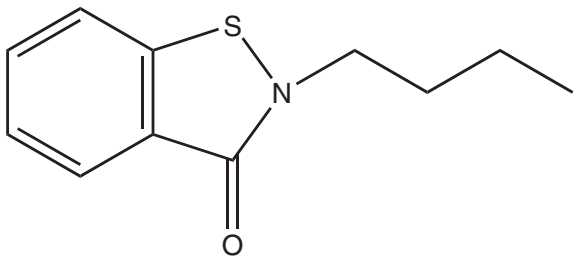


Fig. 1. Chemical structure of *N*-butyl-1,2-benzisothiazolin-3-one, CAS no. 4299-07-4.

To pinpoint the potential allergen(s), the producer of the metalworking fluid was contacted, and asked to provide the ingredients of the suspected product. Separate ingredients were not offered but, instead, six solutions from the different steps in the production of the metalworking fluid were provided. For each solution, it was stated which ingredients were added step-by-step. The solutions obtained from the producer were diluted to 5.0% and 0.5% in water, as described by the producer. In addition to the different solutions, the separate ingredients

Correspondence: Jakob Dahlin, Department of Occupational and Environmental Dermatology, Skåne University Hospital, S-205 02, Malmö, Sweden. Tel: +46 40 336545; Fax: +46 40 336213. E-mail: Jakob.dahlin@skane.se

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Table 1. Patch test results for the metalworking fluid and various isothiazolinones

Test substance	Concentration	D3	D7
Own metalworking fluid, unknown use concentration	50.0%	+	–
	5.0%	–	–
Own metalworking fluid, unknown use concentration	'as is'	++	ND
	50.0%	+	ND
	25.0%	+	ND
	12.5%	–	ND
Own metalworking fluid, fresh unused concentrate	15.0%	(+)	ND
Own metalworking fluid 13% (from machine)	'as is'	+	ND
Own metalworking fluid 6% (fresh)	'as is'	(+)	ND
MCI/MI	200 ppm	–	–
MI	2000 ppm	–	–
MCI	150 ppm	–	–
Benzisothiazolinone	0.05%*	–	–
Octylisothiazolinone	1000 ppm*	–	–
Solution no. 5	5.0%	++	ND
	0.5%	+	ND
Solution no. 6	5.0%	++	ND
	0.5%	+	ND
BBIT	0.05%*	++	ND
	0.005%*	(+)	ND
BBIT	0.05%†	+	ND
	0.005%†	+	ND
BBIT, dilution series	500 ppm†	++	ND
	158 ppm†	++	ND
	50 ppm†	++	ND
	15.8 ppm†	+	ND
	5 ppm†	+	ND
	1.58 ppm†	–	ND

BBIT, N-butyl-1,2-benzisothiazolin-3-one; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; ND, not done.
Vehicle is aq.
*Vehicle is pet.
†Vehicle is ethanol.

specified by the producer and material safety data sheet (MSDS) for the metalworking fluid were obtained, and tested as separate compounds. These included 1-phenoxy-2-propanol (TCI Europe NV, Zwijndrecht, Belgium) diluted to 1.0% in pet., 1-amino-2-propanol (Sigma Aldrich Chemie, Stenheim, Germany) diluted to 1.0% in pet., 2-amino-2-methylpropanol (Sigma Aldrich Co., St Louis, MO, USA) diluted to 1.0% in pet., *N*-methyldiethanolamine (Sigma Aldrich Chemie) diluted to 1.0% in pet., and BBIT (Chemos GmbH, Regenstauf, Germany) diluted to 0.05% and 0.005% in pet. and 0.05% and 0.005% in ethanol.

Positive reactions were obtained on D3 for two of the six solutions, namely solution nos. 5 and 6 (Table 1 and Fig. 2). For solution no. 5, a preservative had been added to the metalworking fluid base, and for solution no. 6, a preservative and an odorant had been added. No reactions were seen for solutions lacking a preservative. Positive reactions were also obtained for BBIT (Table 1 and Fig. 2).

Twenty controls were tested with the diluted metalworking fluid at 50% aq., and none of them reacted. Twenty controls were also tested with BBIT at 0.005% in ethanol, but no positive reactions were observed.

Discussion

Metalworking fluids are well-known causes of occupational dermatitis (1). They are mostly composed as oil–water mixtures, containing both irritants and allergens such as surfactants, alkanolamines, and preservatives (2). The pH value is often high. Metalworking fluids are ideally used in closed systems in a modern workshop with CNC turning machines, but skin contact with the fluid may occur when workpieces are mounted and dismounted in the machines, or when the worker has to perform various measurements or use compressed air to clean the piece.

Isothiazolinone preservatives are well known as contact allergens. In most baseline series, the methyl-

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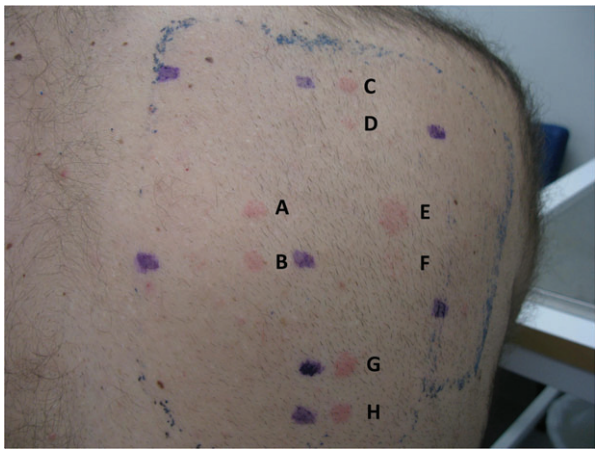


Fig. 2. Patch test reactions for metalworking fluids and *N*-butyl-1,2-benzisothiazolin-3-one (BBIT). A: solution no. 5, 5.0% aq. B: solution no. 5, 0.5% aq. C: solution no. 6, 5.0% aq. D: solution no. 6, 0.5% aq. E: BBIT, 0.05% pet. F: BBIT, 0.005% pet. G: BBIT, 0.05% ethanol. H: BBIT, 0.005% ethanol.

chloroisothiazolinone/methylisothiazolinone mixture is tested, and nowadays methylisothiazolinone is also tested as a separate preparation. In the oil and cooling fluid series, benzisothiazolinone and octylisothiazolinone are usually included. BBIT is a preservative that has previously not been reported as a contact allergen in metalworking fluids. A small survey of MSDSs on the internet showed that this preservative may be present not only in metalworking fluids, but also in wallpaper adhesives, epoxy resins, and silicone sealants. BBIT is listed as a possible contact allergen according to risk phrases used in the MSDS. In the MSDS for the cooling fluid obtained from the workplace, BBIT was not declared to be present in the metalworking fluid, but its presence as the only preservative added was confirmed by the manufacturer.

No reports of contact dermatitis caused by BBIT or contact allergy to BBIT (Fig. 1) were found in the literature. In a guinea-pig maximization test (GPMT), BBIT was found not to induce sensitization (3). In another study, BBIT was considered to be a weak contact allergen in the GPMT, but this could not be confirmed with a murine local lymph node assay (4). No cross-reactions to BIT in the oil and cooling fluid series or other isothiazolinones could be shown in this case (Table 1).

The present case shows the importance of testing the products actually used at the workplace. In this case, positive reactions were obtained neither with the baseline series nor with the oil and cooling fluid series. It also shows that an MSDS does not reliably provide complete information regarding allergens, as they may be present in concentrations that may be lower than the declaration limit. BBIT may be considered for inclusion in the oil and cooling fluid series, as well as in other series used for patch testing.

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